Community Blood Center
Community Tissue Services

www.cbccts.org

MAIN OFFICE

349 South Main St.
Dayton, Ohio 45402-2715
1-800-388-4483
(937) 461-3450
FAX (937) 461-9217

BLOOD CENTERS

105 South D St.
Hamilton, Ohio 45013
(513) 894-6966
FAX (513) 894-4901

3990 Roosevelt Blvd. Suite C
Middletown, Ohio 45044
(513) 727-1995
FAX (513) 727-0006

4821 Old National Rd. East
Richmond, Indiana 47374
(765) 962-6329
FAX (765) 966-3957

2200 North Limestone St.
Suite 106
Springfield, Ohio 45503
(937) 399-2611
FAX (937) 399-5044

TISSUE CENTERS

349 South Main St.
Dayton, Ohio 45402-2715
1-800-684-7783
FAX/OFFICE (937) 461-4225

328 S. Adams Street
Fort Worth, Texas 76104
1-800-905-2556
(817) 332.1898
FAX (817) 332.1958

3425 North First St.
Suite 103
Fresno, California 93726
1-800-201-8477
FAX (559) 229-7217

3450 N. Meridian St.
Indianapolis, Indiana 46208
1-800-984-7783
FAX (317) 916-5255

16361 N.E. Cameron Blvd.
Portland, Oregon 97230
1-800-545-8668
FAX (503) 408-9395

August 17, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

To Whom It May Concern:

Community Blood Center/Community Tissue Services (CBC/CTS) appreciates the opportunity to comment on the Draft Guidance for Industry entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (Guidance).

CBC/CTS's Tissue Services (CTS) were founded in Dayton, Ohio in 1986. CTS has grown into a national network with branches located in Portland, Oregon; Fresno, California; Indianapolis, Indiana; Toledo, Ohio; Philadelphia, Pennsylvania, and Ft. Worth, Texas. Currently, CTS distributes more than 30,000 allografts annually, making it one of the largest tissue banks in the United States. As a full service tissue bank, CTS is strongly committed to providing quality tissue for transplantation. Patient safety and physician satisfaction are our priorities. All CTS branches are accredited by the American Association of Tissue Banks (AATB) or are in the process of being accredited. The AATB Standards are followed by all CTS branches. Compliance with these standards is monitored by our Quality Assurance department.

CTS is very supportive of the efforts of the FDA to make HCT/Ps safer, and we feel we have been proactive in our approach to tissue safety. Like many tissue banks, this Guidance will have little effect on our policies and procedures, since we are already in substantial compliance with relevant sections. However, there is certain specific language in the Guidance Document regarding sepsis and related terms that is confusing and to some extent contradictory. We feel that the simple appearance or presence of the word "sepsis" (or related terms) in a medical record should not, in and of itself, preclude donor eligibility for collection of HCT/Ps. Other sections of the Guidance give more flexibility in determining whether sepsis exists or is at a stage where risk of bacterial transmission is possible.

Sepsis

As listed in this Guidance, we agree that:

- There is a risk of transmission of any agent causing sepsis because *it is potentially transmissible by HCT/Ps and it has sufficient incidence and/or prevalence to affect the potential donor population.*
- That donors should be ineligible if there is *known or suspected sepsis at the time of death.*

2004D-0193 C5

This position is supported by other organizations including the AATB and its members. The current AATB Standard, D4.310, reads as follows:

> The Medical Director or licensed physician designee shall not release allogeneic cells and/or tissue for transplantation from donors who exhibit any of the following findings: 1) Evidence detected by history, physical examination, laboratory, laboratory testing or autopsy, of significant active infection at the time of donation, including septicemia, systemic viral disease (including HIV infection and viral hepatitis), untreated syphilis, clinically active tuberculosis, leprosy (Hansen's disease), or systemic mycosis.

However, we have concerns about certain recommendations in this Guidance that are based on recent clinical literature. Though mortality as the result of sepsis is relatively high, the majority of patients with sepsis recover with treatment and survive. Also, many who may succumb to the complications of their septic episode are no longer bacteremic nor do they have an active communicable infectious agent. Others with sepsis are appropriately treated, but then die of underlying diseases or unrelated conditions. While septicemia, sepsis syndrome, systemic infection, and septic shock would undeniably necessitate donor deferral when associated with bacteremia, it is less clear whether these donors should be deferred once the specific bacterial pathogen has been cleared due to adequate treatment with antimicrobials.

The Guidance characterizes sepsis as *including, but not limited to bacteremia, septicemia, sepsis syndrome, systemic infection and septic shock.* The Guidance also states, *if bacteremia, septicemia, sepsis syndrome, systemic infection or septic shock is specifically noted in the medical records, the donor is ineligible.* The text continues as follows:

Sepsis is often described by the following clinical evidence, but we recommend that these signs be considered in light of other information obtained about the donor in making a donor eligibility determination.

- *Clinical evidence of infection; and*
- *Two or more of the following systemic responses to infection if unexplained:*
  - *Temperature of >100.4° F (38° C);*
  - *Heart rate >90 beats/min;*
  - *Respiratory rate >20 breaths/min or PaCO2 <32; or*
  - *WBC >12,000 cells/mm3, <4,000 cells/mm3, or >10% immature (band) forms.*
- *More severe signs of sepsis include unexplained hypoxemia, elevated lactate, oliguria, altered mentation, and hypotension.*
- *Positive (pre-mortem) blood cultures may be associated with the above signs.*

We feel this may be an overly broad and vague characterization as it relates to donor eligibility for procurement of HCT/Ps. The above signs and symptoms can be present in numerous situations, and particularly when potential donors have multiple disease processes and conditions. The clinical symptoms and signs of true sepsis are mimicked by many conditions and diseases. When diagnosing a very sick patient, ruling out sepsis is a common action. Since sepsis is such a serious diagnosis, and can have dire

consequences, empiric treatment is frequently initiated before an absolute diagnosis can be confirmed.

Caution must be taken during diagnosis, as other situations can mimic sepsis. For example:

- Neurologic injuries lead to elevated temperatures and WBC counts (including elevated band forms), as well as altered mentation and hypotension.
- Metabolic diseases can lead to abnormalities of heart and respiration rate, with accompanying blood chemistry abnormalities.

More commonly, a combination of multiple disease processes and conditions, along with confounding factors such as trauma, results in clinical laboratory findings like those seen with sepsis. This often leads to consideration of sepsis in the differential diagnosis during the hospital stay. Work-up of the diagnosis may take days, and, during that time, the diagnosis of sepsis is noted numerous times throughout the medical record even in cases where sepsis is ruled out.

In the case where sepsis on admission is likely or confirmed, there are still situations we feel that donors should be eligible for procurement of HCT/Ps. A donor should be eligible if the donor:

- Has been appropriately treated with antimicrobials for a time long enough to render the donor non-bacteremic;
- Has normal or baseline-appropriate clinical signs (temperature, pulse, respiration);
- Has had symptomatic improvement;
- Has normal, improving, or explainable abnormal laboratory parameters; and,
- Has a clearly established non-infectious cause of death.

Bacteremia

It must also be noted that bacteremia is not necessarily synonymous with sepsis. Transient bacteremia is common in a number of situations, such as after dental or minor surgical procedures, and after some activities of daily living such as brushing teeth. Bacteria, in most cases, are rapidly cleared from the circulation and neutralized by the immune system, with no clinically significant sequellae. It is also likely that bacteremia is present after severe trauma and as a result of a prolonged hypoxic/ischemic event before death. Years of historical data support that carefully screened donors in these situations are safe in terms of donations of HCT/Ps.

Evaluation of Donor Eligibility

The prospective donor's treating physicians may not be in the best position to evaluate donor eligibility. The clinician's opinions are frequently based on incomplete or inaccurate information, particularly in emergency situations or when numerous tests and procedures have been performed in the agonal period. Medical record documentation may lag far behind evaluation and treatment, and, in some cases, long after the death of the patient. For example, final results of blood cultures that were obtained in the hospital may not be known to the treating physician but may be obtained by the tissue bank personnel doing donor eligibility determination.

In many instances, the Tissue Bank Medical Director, with the ability to review completed records and supplementary information such as autopsy reports, procurement culture results, and input from donor's private physician information is in a much better position to evaluate significant infectious disease and sepsis. Tissue banks also have the advantage of time, which allows for seeking and collecting additional medical information, if necessary. In some cases, tissue bank medical directors are in a position to make a more definitive, true diagnosis.

West Nile Virus

A related concern involves evaluation and deferral for suspected West Nile Virus. We feel that fever and headache during the seven days prior to death without consideration of the entire medical condition should not automatically defer a potential donor of HCT/Ps.

The Guidance (Section III. E. 16.) recommends that cadaveric donors be deemed ineligible if they *have had both a fever and a headache (simultaneously) during the 7 days before donation*. We feel this is unnecessarily restrictive since many diseases and conditions include these findings. To consider only these two findings without consideration of all of the other information available to tissue banks will defer many otherwise acceptable donors.

In summary, we would suggest that current language in the AATB Standards is sufficient to address most FDA concerns regarding sepsis. However, even though we are in substantial agreement with this Guidance regarding sepsis and WNV infection, we recommend the following changes:

1. Section III. F. 7: *If bacteremia, septicemia, sepsis syndrome, systemic infection or septic shock is specifically noted in the medical records, the donor is ineligible.*

    - We feel that the Guidance should read as follows: **If known or suspected bacteremia, septicemia, sepsis syndrome, systemic infection or septic shock is present at the time of death, the donor is ineligible.**

      This is consistent with verbiage used in other areas of the document, and it correctly defers evaluation of the potential donor's eligibility to the "responsible person" which, in our case, would be the four full time Medical Directors at CTS. We feel it may be appropriate to further specify characteristics of the "responsible person" who makes the ultimate eligibility decision that leads to processing and distribution of tissue.

2. Section III. E. 16: Recommends that cadaveric donors be ineligible if they *have had both a fever and a headache (simultaneously) during the 7 days before donation.*

   We feel that a better statement would read as follows: **Cadaveric donors are ineligible if they have had unexplained fever and a headache (simultaneously) during the 7 days prior to death.**

Again, Community Blood Center/Community Tissue Services appreciates the opportunity to comment on the proposed Donor Eligibility Guidance. We request that FDA take our comments into consideration prior to finalizing the document.

Sincerely,

David Smith, M.D.
Medical Director, Tissue Services